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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/711,896	11/15/2000	Tohru Kayano	KAYANO 1	8185

7590 06/13/2005

Browdy and Neimark
624 Ninth Street N W
Washington, DC 20001-5303

EXAMINER	
DEVI, SARVAMANGALA J N	
ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 06/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/711,896	KAYANO ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,6-25 and 27* is/are pending in the application.

4a) Of the above claim(s) *10-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,6-9,24,25 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Sequence report (1)*.

RESPONSE TO APPLICANS' AMENDMENT

Applicants' Amendment

1) Acknowledgment is made of Applicants' amendment filed 03/28/05 in response to the non-final Office Action mailed 09/29/04.

Status of Claims

2) Claims 1 and 4 have been amended via the amendment filed 03/28/05.

New claim 27 has been added via the amendment filed 03/28/05.

Claim 5 has been canceled via the amendment filed 03/28/05.

Claims 1, 4, 6-25 and 27 are pending.

Claims 1, 4, 6-9, 24, 25 and 27 are under examination.

Prior Citation of Title 35 Sections

3) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

4) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Rejection(s) Moot

5) The rejection of claim 5 made in paragraph 14(c) of the Office Action mailed 09/29/04 under 35 U.S.C. § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claim.

6) The rejection of claim 5 made in paragraph 23 of the Office Action mailed 01/21/04 and maintained in paragraph 11 Office Action mailed 09/29/04 under 35 U.S.C. § 103(a) as being unpatentable over Yong *et al.* (*Immunological Journal* 15: 226-228, October 1999 - original and English translation) in view of Campbell AM (*In*: *Monoclonal Antibody Technology*. Elsevier Science Publishers, The Netherlands, Chapter 1, pages 1-32, 1984), is moot in light of Applicants' cancellation of the claim.

7) The rejection of claim 5 made in paragraph 14(e) of the Office Action mailed 09/29/04 under 35 U.S.C. § 112, second paragraph, as being indefinite, is moot in light of Applicants'

cancellation of the claim.

8) The rejection of claim 5 made in paragraph 15 of the Office Action mailed 09/29/04 under 35 U.S.C. § 102(b) as being anticipated by Akita *et al.* (*J. Biol. Chem.* 272: 26595-26603, October 1997 - already of record), is moot in light of Applicants' cancellation of the claim.

Rejection(s) Withdrawn

9) The rejection of claims 1, 4, 6-8 and 24 made in paragraph 23 of the Office Action mailed 01/21/04 and maintained in paragraph 11 Office Action mailed 09/29/04 under 35 U.S.C. § 103(a) as being unpatentable over Yong *et al.* (*Immunological Journal* 15: 226-228, October 1999 - original and English translation) in view of Campbell AM (*In*: *Monoclonal Antibody Technology*. Elsevier Science Publishers, The Netherlands, Chapter 1, pages 1-32, 1984), is withdrawn in light of Applicants' amendment to the claims and/or the base claim(s). A modified rejection is set forth below to reject the claims, as amended.

10) The rejection of claims 9 and 25 made in paragraph 24 of the Office Action mailed 01/21/04 and maintained in paragraph 12 Office Action mailed 09/29/04 under 35 U.S.C. § 103(a) as being unpatentable over Yong *et al.* (*Immunological Journal* 15: 226-228, October 1999 - original and English translation) as modified by Campbell AM (*In*: *Monoclonal Antibody Technology*. Elsevier Science Publishers, The Netherlands, Chapter 1, pages 1-32, 1984) as applied to claims 1 and 24 above, is withdrawn in light of Applicants' amendment to the claims and/or the base claim(s). A modified rejection is set forth below to reject the claims, as amended.

11) The rejection of claim 1 and those that depend therefrom made in paragraph 13 of the Office Action mailed 09/29/04 under 35 U.S.C. § 112, first paragraph, as containing new subject matter, is withdrawn in light of Applicants' amendment to the claim.

12) The rejection of claim 1 made in paragraph 14(a) of the Office Action mailed 09/29/04 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

13) The rejection of claim 1 made in paragraph 14(b) of the Office Action mailed 09/29/04 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

14) The rejection of claim 4 made in paragraph 14(c) of the Office Action mailed 09/29/04

under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

15) The rejection of claim 1 made in paragraph 14(d) of the Office Action mailed 09/29/04 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

16) The rejection of claims 4, 6-9, 24 and 25 made in paragraph 14(e) of the Office Action mailed 09/29/04 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the base claim.

17) The rejection of claims 1, 4, 6, 24 and 25 made in paragraph 15 of the Office Action mailed 09/29/04 under 35 U.S.C. § 102(b) as being anticipated by Akita *et al.* (*J. Biol. Chem.* 272: 26595-26603, October 1997 - already of record), is withdrawn in light of Applicants' amendment to the base claim.

18) The rejection of claim 9 made in paragraph 16 of the Office Action mailed 09/29/04 under 35 U.S.C. § 103(a) as being unpatentable over Akita *et al.* (*J. Biol. Chem.* 272: 26595-26603, October 1997) as applied to claim 1 above, is withdrawn in light of Applicants' amendment to the base claim.

New Rejection(s) Based on Applicants' Amendment

The new rejections set forth below are necessitated by Applicants' amendments to the claims, and/or the base claim(s), which change the scope of the claims.

Rejection(s) under 35 U.S.C. § 112, First Paragraph (New Matter)

19) Claim 1 and those that depend therefrom are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 1, as amended, is directed to an isolated antibody specific to 'a polypeptide comprising the amino acid sequence of SEQ ID NO: 1, wherein said antibody does not recognize mature human interleukin-18'. The claimed antibody is now required to absolutely not recognize mature human interleukin-18. Applicants point to first full paragraph on page 32 of the specification as providing descriptive support for the added limitations. However, a review of

this part of the specification shows that there is no descriptive support for the added limitations. The first full paragraph of page 32 of the specification as originally filed states as follows:

> The monoclonal antibodies obtained in this Example were subjected to enzyme-immunoassay as described in Example 1-3(b). These monoclonal antibodies exhibited an immunoreactivity against human IL-18 precursor but not **apparently** against human IL-18. Thus 15 types of the present antibody were obtained. One of the monoclonal antibody belonging to the class IgG_{2b} whose immunoreactivity against IL-18 precursor **was particularly high**, in this assay, was named "mAb-proHuIL18#75". [Emphasis added]

The above-cited paragraph does not provide descriptive support for an isolated antibody specific to 'a polypeptide comprising the amino acid sequence of SEQ ID NO: 1, wherein said antibody **does not** recognize mature human interleukin-18'. Terms such as 'apparently' and 'particularly high' when evaluated together with what is described in Example 1-3(b) indicate that an isolated antibody that is exclusively specific to a polypeptide comprising the amino acid sequence of SEQ ID NO: 1 and which absolutely does not recognize mature human interleukin-18, is not described in the instant specification. Furthermore, the description on page 34 and at paragraph bridging pages 34 and 35 of the specification, and the results from Figure 3 of the specification indicate that both the first and second antibodies of the instant invention showed some level of immunoreactivity with human IL-18, but were not totally free of immunoreactivity with human IL-18. Therefore, the new limitations in the instant claims are considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after 608.04(c).

Applicants are invited to point to specific line and page numbers of the specification, as originally filed, that provide descriptive support for the limitations identified above, or to remove the new matter from the claim(s).

Rejection(s) under 35 U.S.C. § 103

20) Claims 1, 4-8 and 24 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Yong *et al.* (*Immunological Journal* 15: 226-228, October 1999 - original and English translation, already of record) or Tanimoto *et al.* (US 5,891,663) in view of Campbell AM (*In*: *Monoclonal Antibody Technology*. Elsevier Science Publishers, The Netherlands, Chapter 1, pages 1-32, 1984, already of record).

Yong *et al.* taught a purified recombinant human interleukin-18 precursor expressed in *E.*

coli via a recombinant plasmid, pQEIL 18p. Yong *et al.* identified a 36 amino acid-long amino terminal end of hIL-18 precursor protein to be an unusual leader sequence. This leader sequence of the prior art is structurally identical to the instantly recited SEQ ID NO: 1 (see entire document, especially pages 5, 6, 8, 10 and 11; and Figures 1 and 2).

Tanimoto *et al.* disclosed a purified precursor IFN gamma polypeptide comprising an N-terminal fragment having the amino acid sequence, or the N-terminal fragment which shows 100% sequence identity with the instantly recited SEQ ID NO: 1. The precursor polypeptide does not induce IFN-gamma induction in immunocompetent cells. See first and second full paragraphs in column 3; Example 4-3; SEQ ID NO: 1 in columns 13 and 14; and the attached sequence alignment report.

Yong *et al.* or Tanimoto *et al.* do not teach an isolated antibody specific to the polypeptide of SEQ ID NO: 1 wherein the antibody does not recognize mature interleukin 18.

However, methods of producing antibodies to a specific polypeptide or a portion thereof, were well known in the art at the time of the invention. Furthermore, Campbell taught that it is customary now for any group working on a macromolecule to both clone the genes coding for it and make antibodies to it sometimes 'without a clear objective for their application'. Campbell also taught that protein molecules can be studied in the field of research using these antibodies (see page 29, last paragraph).

Given that the structure of the polypeptide portion comprising 36 amino acid-long amino terminal end of hIL-18 precursor protein was already known and identified in the art by Yong *et al.* or Tanimoto *et al.*, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to generate or isolate a monoclonal antibody, polyclonal antibody, or a hybridoma cell line specific to Yong's unusual leader sequence of SEQ ID NO: 1 or Tanimoto's SEQ ID NO: 1, using art-known antibody production or hybridoma techniques, to produce the isolated antibody or hybridoma of the instant invention, with a reasonable expectation of success. The resultant antibody produced using Yong's specific 36 amino acid-long leader sequence or Tanimoto's amino acid sequence of SEQ ID NO: 1 as the immunogen is expected to be specific to the leader sequence or to SEQ ID NO: 1, and is expected to not bind to mature interleukin 18, since mature interleukin-18 was not the immunogen used to raise the antibody. Given Campbell's teaching that antibodies to a protein are made in the art without a clear objective for their application, one of skill in the art would have been *motivated* to produce

the instant invention for the expected benefit of producing an antibody to Yong's 36 amino acid-long amino terminal portion of hIL-18 precursor protein or Tanimoto's amino acid sequence of SEQ ID NO: 1 in order to study the protein portion or the unusual leader sequence for research purposes as taught by Campbell.

Claims 1, 4-8 and 24 are *prima facie* obvious over the prior art of record.

21) Claims 9 and 25 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Yong *et al.* (*Immunological journal* 15: 226-228, October 1999 - original and English translation, already of record) or Tanimoto *et al.* (US 5,891,663) as modified by Campbell AM (*In*: *Monoclonal Antibody Technology*. Elsevier Science Publishers, The Netherlands, Chapter 1, pages 1-32, 1984, already of record) as applied to claims 1 and 24 above.

The teachings of Yong *et al.* or Tanimoto *et al.* as modified by Campbell do not teach an immunoassay kit comprising an isolated antibody as recited, or the antibody contained in a physiologically acceptable carrier.

However, methods of assembling an immunoassay kit using an antibody product was well known and routinely practiced in the art, and would have been obvious to a skilled artisan at the time the invention was made to produce such an immunoassay kit for diagnostic purposes using the antibody of Yong *et al.* or Tanimoto *et al.* as modified by Campbell *et al.* One of skill in the art would have been motivated to produce the instant invention for the expected benefit of making readily available the prior art antibody, or for commercializing the prior art antibody for diagnostic use, since it is routine and conventional to use antibody reagents in immunoassay kits.

Similarly, adding a physiologically acceptable carrier to an antibody is routine and very conventionally practiced in the art. Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to add an art-known pharmaceutical carrier to the prior art antibody of Yong *et al.* or Tanimoto *et al.* as modified by Campbell *et al.* to produce the instant invention with a reasonable expectation of success, since it is quite conventional to have an antibody mixed with in a pharmaceutical or physiologically acceptable carrier for diagnostic purposes.

Claims 9 and 25 are *prima facie* obvious over the prior art of record.

Response to Applicants' Arguments on Yong's Teachings

22) With regard to the teachings of Yong *et al.*, Applicants contend that Yong *et al.* do not

disclose or teach an antibody that recognizes the IL-8 precursor, i.e., the leader sequence, but which does not recognize the mature IL-18 protein. Applicants argue that neither Yong *et al.* nor Campbell suggests preparation of an antibody that recognizes only the precursor of IL-18 protein by using the leader sequence of a protein. Applicants submit that one of skill in the art may obtain antibodies which recognize the IL-18 precursor if such a person uses the recombinant IL-18 precursor disclosed by Yong *et al.* as an antigen following Campbell's teaching. Applicants argue that many of the thus obtained antibodies also would recognize the mature IL-18 protein and that it would then become necessary to select antibodies that do not recognize the mature IL-18 protein from among the many antibodies obtained in order to arrive at the antibody claimed in the amended claim 1. Applicants assert that Campbell does not teach such selection. Applicants point to specific parts of the instant specification and state that an antibody obtained by using mature IL-18 as antigen recognizes the IL-18 precursor as well as mature IL-18.

Applicants' arguments have been carefully considered, but are non-persuasive. First, if Yong *et al.* taught an antibody that recognizes the IL-8 precursor, i.e., the leader sequence, but which does not recognize the mature IL-18 protein, Yong *et al.* would have been applied as prior art under 35 U.S.C. § 102 as opposed to 35 U.S.C. § 103. As Applicants readily acknowledge, one of skill in the art would obtain antibodies that recognize the IL-18 precursor by using the recombinant IL-18 precursor disclosed by Yong *et al.* as an antigen and Campbell's teaching. *Arguendo*, even if the resultant antibodies contained a mixture of antibodies including those recognizing mature IL-18 protein, as alleged, it is well within the realm of routine experimentation to separate two antibody populations with two different specificities using art-known affinity separation techniques and to isolate the antibody having the specificity recited in the instant base claim. Selection of an antibody of a particular specificity from a pool or mixture of antibodies of diverse immunospecificities does not require undue experimentation by one of ordinary skill in the art, since methods of selecting specific antibodies from a polyclonal or monoclonal mixture are well known and routinely practiced in the art. Nothing in Yong *et al.* or Campbell teaches that an antibody obtained using the IL-18 precursor, or the unusual leader sequence having the exact identical structure of the instantly recited SEQ ID NO: 1, would not be specific to SEQ ID NO: 1, or would also recognize mature IL-18. The references of Yong *et al.* and Campbell are properly applied under 35 U.S.C. § 103. See paragraphs 20 and 21 above.

Remarks

23) Claims 1, 4-9, 24 and 26 stand rejected.

24) Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. **THIS ACTION IS MADE FINAL.** Applicants are reminded of the extension of time policy as set forth in 37 C.F.R 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

25) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center, which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The central Fax number for submission of amendments, responses or papers is (703) 872-9306.

26) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

27) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

June, 2005

S. DEVI, PH.D.
PRIMARY EXAMINER

SEQ ID NO. 1.

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RESULT 2
US-08-896-501A-1
; Sequence 1, Application US/08896501A
; Patent No. 5891663
;  GENERAL INFORMATION:
;    APPLICANT:  TANIMOTO, Tadao
;    APPLICANT:  KURIMOTO, Masashi
;    TITLE OF INVENTION:  PROCESS FOR PRODUCING POLYPEPTIDE
;    NUMBER OF SEQUENCES:  9
;    CORRESPONDENCE ADDRESS:
;      ADDRESSEE:  BROWDY AND NEIMARK
;      STREET:  419 Seventh Street, N.W., Suite 300
;      CITY:  Washington
;      STATE:  D.C.
;      COUNTRY:  USA
;      ZIP:  20004
;    COMPUTER READABLE FORM:
;      MEDIUM TYPE:  Floppy disk
;      COMPUTER:  IBM PC compatible
;      OPERATING SYSTEM:  PC-DOS/MS-DOS
;      SOFTWARE:  Patent In Release #1.0, Version #1.30
;    CURRENT APPLICATION DATA:
;      APPLICATION NUMBER:  US/08/896,501A
;      FILING DATE:  18-JUL-1997
;    PRIOR APPLICATION DATA:
;      APPLICATION NUMBER:  JP 213,267/1996
;      FILING DATE:  25-JUL-1996
;    PRIOR APPLICATION DATA:
;      APPLICATION NUMBER:  JP 31,474/1997
;      FILING DATE:  31-JAN-1997
;    ATTORNEY/AGENT INFORMATION:
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;      TELEFAX:  202-737-3528
;  INFORMATION FOR SEQ ID NO:  1:
;    SEQUENCE CHARACTERISTICS:
;      LENGTH:  41 amino acids
;      TYPE:  amino acid
;      STRANDEDNESS:  single
;      TOPOLOGY:  linear
;    MOLECULE TYPE:  peptide
;    FRAGMENT TYPE:  N-terminal fragment
US-08-896-501A-1

  Query Match           100.0%;  Score 188;  DB 2;  Length 41;
  Best Local Similarity  100.0%;  Pred. No. 3.4e-21;
  Matches   36;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 MAAEPVEDNCINFVAMKFIDNTLYFIAEDDENLESD 36
              |||||||||||||||||||||||||||||||||||||
Db          1 MAAEPVEDNCINFVAMKFIDNTLYFIAEDDENLESD 36
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